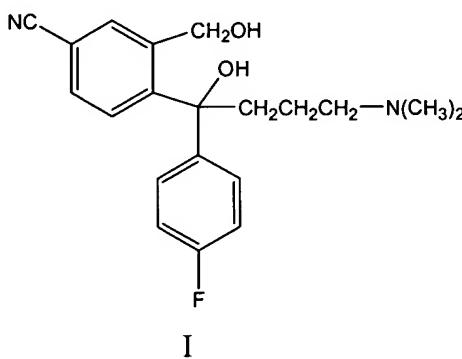
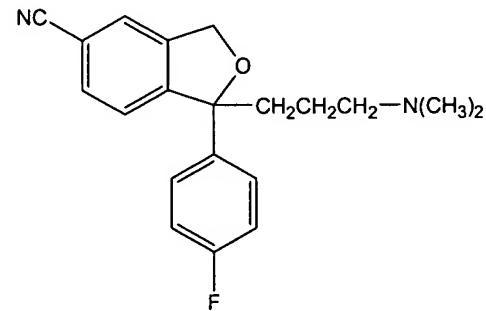


**What is claimed is:**

1. A method for the preparation of citalopram and its salts, which is characterized by: citalopram diol intermediate is crystallized one or more times in the form of precipitate, the obtained crystal of Formula I is subjected to ring closure by dehydration to give citalopram of Formula II, or citalopram is further converted into citalopram salts.



I



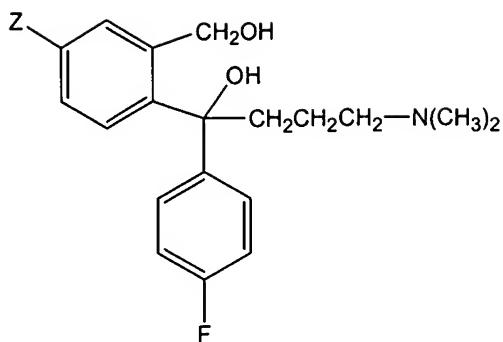
II

10 2. A method for the preparation of S-citalopram and its salts, which is characterized by: citalopram diol intermediate is crystallized one or more times in the form of precipitate to give citalopram diol intermediate alkali crystal, the obtained crystal is subjected to resolution and ring closure by dehydration to give S-citalopram, or S-citalopram is further converted into S-citalopram salts.

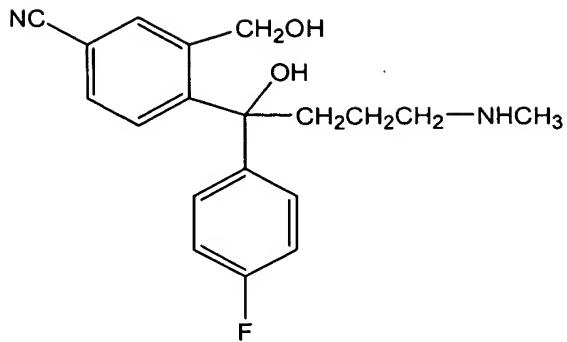
15 3. The method of Claim 2 characterized by: the prepared citalopram diol intermediate of Formula I is resolved to give R- and/or S-citalopram diol intermediate free alkali, or their mixture, or their corresponding acid addition salts.

20 4. The method of Claim 1 or 2 characterized by: citalopram diol intermediate free alkali of Formula I is separated from the impurities contained in the crude salt or crude mixture of citalopram diol intermediate alkali so that it is purified.

25 5. The method of Claim 1 or 2 characterized by: citalopram diol intermediate alkali is precipitated in the form of crystal, recrystallized one or more times and /or converted into its salts so that one or more impurities of Formula III and/or IV contained in the crude salt or crude mixture is eliminated:



III



IV

5 In Formula III, Z is halogen;  $-\text{O}-\text{SO}_2-(\text{CF}_2)_n-\text{CF}_3$ , wherein n is 0~8;  $-\text{CHO}$ ;  $-\text{NHR}^1$ ;  
 -COOR<sup>2</sup>; -CONR<sup>2</sup>R<sup>3</sup>; wherein R<sup>2</sup> and R<sup>3</sup> is hydrogen, alkyl, any substitutional aryl or arylalkyl,  
 R<sup>1</sup> is hydrogen or alkylcarbonyl.

10 6. The method of any of the Claims 4-6 characterized by: the crude salt or crude mixture of  
 citalopram diol intermediate alkali is primarily purified before it is precipitated in the form of  
 crystal.

15 7. The method of any of the Claims 4-6 characterized by: citalopram diol intermediate alkali is set  
 free from the crude salt or crude mixture and further purified before it is precipitated in the form of  
 crystal.

8. A method for the preparation of R- or S-citalopram free alkali and its acid addition salts, which  
 is characterized by: through the resolution of the mixture of S- and R- citalopram diol intermediate  
 with more than 50% of one of the enantiomers, racemic citalopram diol intermediate free alkali and  
 R- or S-citalopram diol intermediate free alkali are obtained. The method includes following steps:

20 (1) Citalopram diol intermediate is precipitated or crystallized from the solution or the solventless  
 oil substance in the form of free alkali;

(2) The precipitate or crystal is separated from the mother liquor or the oil substance;

25 (3) The remained citalopram diol intermediate optical enantiomers in the mother liquor or the oil  
 citalopram diol intermediate optical enantiomers are resolved and their optical rotation are  
 improved. Then S- or R-citalopram diol intermediate is separated from the mother liquor. Or the  
 obtained solvent less oil alkali is converted into S- or R-citalopram through ring closure, S- or  
 R-citalopram is further converted into its acid addition salts. Wherein, S-citalopram diol  
 intermediate is converted into S-citalopram through proper ring closure reaction, R-citalopram diol  
 intermediate is converted into the mixture of S-citalopram and R-citalopram through proper ring  
 closure reaction.

30 9. A method for the preparation of R- citalopram free alkali or S- citalopram free alkali and its  
 acid addition salt, which is characterized by: through the resolution of the mixture of S- and R-  
 citalopram diol intermediate with more than 50% of one of the enantiomers, racemic citalopram  
 diol intermediate salt and R- or S- citalopram diol intermediate salt are obtained. The method

includes the following steps:

(1) Citalopram diol intermediate is precipitated or crystallized from the solution in the form of salt;

(2) The precipitate or crystal is separated from the mother liquor;

5 (3) The remained citalopram diol intermediate salt optical enantiomers in the mother liquor are purified through resolution, and their optical rotation are improved. Then S-or R-citalopram diol intermediate is separated from the mother liquor and conversed into S-or R-citalopram through ring closure, and finally conversed into its corresponding acid addition salts. Wherein, S-citalopram diol intermediate is conversed into S- citalopram through proper ring closure reaction, R-citalopram diol intermediate is conversed into the mixture of S-citalopram and R-citalopram through proper ring closure reaction.

10 10. The method of Claim 8 for the preparation of R- citalopram free alkali or S-citalopram free alkali and its acid addition salts, which is characterized by:

15 (1) The citalopram diol intermediate among the mixture of S- and R- citalopram diol intermediate is precipitated from the solution or directly crystallized from the oil mixture in the form of free alkali;

(2) The precipitate or crystal is separated from the mother liquor or the oil, and then

20 (3) After separation, the mother liquor or the oil is further subjected to precipitation or crystallization. Then S- and R- citalopram diol intermediate is separated from the mother liquor and further subjected to ring closure to give S- and R- citalopram, or the mixture of S- and R-citalopram. The S-citalopram diol intermediate is subjected to ring closure to give S-citalopram, and S-citalopram can further be conversed into its corresponding acid addition salts.

25 11. The method of Claim 9 for the preparation of R-citalopram free alkali or S-citalopram free alkali and its acid addition salts, which is characterized by:

(1) The citalopram diol intermediate among the mixture of S- and R-citalopram diol intermediate salt mixture is precipitated or crystallized from the solution in the form of salt;

(2) The precipitate or crystal is separated from the mother liquor, and then

30 (3) After separation, the mother liquor is further subjected to precipitation or crystallization. Then S- and R- citalopram diol intermediate salt is separated from the mother liquor and set free as alkali. The alkali is further subjected to ring closure to give S- and R- citalopram, or the mixture of S- and R-citalopram. The S-citalopram diol intermediate is subjected to ring closure to give S-citalopram, and S-citalopram can further be conversed into its corresponding acid addition salts.

35 12. The method of any of the Claims 9-11 characterized by: the mixture of S- and R- citalopram diol intermediate free alkali or salt is obtained through precipitation or crystallization, wherein the ratio of S- and R- citalopram diol intermediate is between 0.8 and 1.2, the preferred ratio is between 0.95 and 1.05, the most preferred ratio is 1.0.

40 13. The method of any of the Claims 1-5 characterized by: citalopram diol intermediate free alkali is directly crystallized from the oil substance to give citalopram diol intermediate free alkali crystal.

14. The method of any of the Claims 1-5 or Claims 11 characterized by: the solvent used can be the proper single component or non-single component solvent that can dissolve citalopram diol intermediate free alkali or the proper mixture of them, or the bicomponent or multicomponent mixture of water and some water soluble solvents of a proper proportion.

5

15. The method of Claim 14 characterized by: the preferred solvents are C<sub>1-4</sub> alcohol , the bicomponent or multicomponent mixture of C<sub>1-4</sub> alcohol and water, C>4 ester, C<sub>3-8</sub> hydrocarbon and/or cycloparaffin, the mixture of C>3 ester and /or cycloparaffin; the more preferred are 60%~90% methanol solution, 60%~90% ethanol solution, isopropyl ether, the mixture of isopropyl ether and hexane; the most preferred are 70% ethanol solution , the mixture of isopropyl ether and hexane (v/v=1:2) , the mixture of isopropyl ether and heptane (v/v=1:2).

10

16. The method of Claim 14 characterized by: the crystallization temperature can be any proper temperature between -40°C and the boiling point of the solvent, the preferred temperature is between -20°C and 60°C, the more preferred is temperature between -5°C and room temperature.

15

17. The method of any of the Claims 1-16 characterized by: citalopram diol intermediate free alkali crystal or its optical enantiomers as well as their acid addition salts with a purity of over 99.6% are prepared.

20

18. The method of the Claims 1-17 characterized by: through ordinary purification, the purity of citalopram free alkali or S- citalopram free alkali and their acid addition salts obtained after ring closure is over 99.5%(w/w), the preferred purity is 99.8%(w/w); wherein, the purity of S-citalopram free alkali and its acid addition salts is over 97%(w/w), the preferred purity is 99%(w/w).

25

19. The method of the Claims 1-18 characterized by: the obtained pure citalopram free alkali or S- citalopram free alkali forms salt with some pharmaceutically acceptable acids either through crystallization or not, to give citalopram salt or S- citalopram salt whose purity is over 99.7%(w/w) and the preferred purity is 99.9%(w/w).

30

20. Citalopram free alkali or S- citalopram free alkali or their salts prepared according to the methods of Claim18 and Claim19, can be directly used for the preparation of the drug.

35

21. Citalopram free alkali or S- citalopram free alkali and their salts prepared according to the methods of Claim 20 are conversed into routine formulations through routine methods by adding some pharmaceutically acceptable adjuvants.

40

22. A crystal alkali of Formula I which is characterized by: a mixture containing both S- and R-enantiomer of Formula I, wherein the ratio of S- and R-enantiomer is between 0.5 and 1.5, the preferred ratio is between 0.8 and 1.2, the most preferred ratio is 1.0, namely racemic crystal alkali.